97. The method of claim 50, wherein the T cell is contacted with the agent *in vitro*.

98. (Amended) A method for modulating responsiveness in an anergic T cell [predetermined to be anergic], comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is modulated.

99. The method of claim 98, wherein the agent stimulates a signal associated with ligation of the cytokine receptor γ chain, such that T cell stimulation occurs.

100. The method of claim 99, wherein the agent acts extracellularly to stimulate a signal associated with ligation of the cytokine receptor γ chain such that the T cell is stimulated.

101. The method of claim 99, wherein the agent is an anti-γ chain antibody.

REMARKS

Claim Amendments

Claims 48-101 remain in the present application. Claim 98 has been amended herein to reduce the number of issues for appeal by replacing the phrase "in a T-cell predetermined to be anergic" with the phrase "an anergic T-cell" thereby addressing certain issues under 35 U.S.C. §112, first and second paragraphs. Support for this amendment can be found in the disclosure, for example, at page 3, lines 26-29.

Applicants respectively submit that the foregoing claim amendment is permissible under 37 C.F. R. § 1.116 as reducing the number of issues for appeal and/or adopting the Examiner's suggestions. Moreover, the foregoing claim amendment requires no new search. Accordingly, Applicants respectively request entry of the present Amendment.

Applicants also wish to state that the claim amendments made herein should in no way be construed as an acquiescence by the Applicants to any of the Examiner's

rejections, as they have been made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute identical or similar claims to those pending prior to amendment herein in the instant or in a subsequent patent application.

Species Election

In paragraph 2 of the subject Office Action, the Examiner states that "as indicated below . . ., methods of modulating unresponsiveness by a T cell is rejected under 35 U.S.C. §112 first and second paragraphs, because it does not clearly recite the intended endpoint of the elected invention, methods of stimulating T cells." In other words, the Examiner asserts that the pending claims are subject to rejection because they are not limited to the elected species of stimulating T cells.

Applicants respectfully traverse this rejection. Under 35 U.S.C. §121, when a generic claim is presented in an application, an election of a single species falling within the presented genus for prosecution on the merits may be required to which the claims will be restricted ***if no generic claim is held allowable***. Therefore, ***prior to requiring restriction of the claims to the elected species, it must be established that no generic claim is allowable.***

In the present case, Applicants have presented a generic claim, encompassing both the claimed species of stimulating and inhibiting a T cell response, which Applicants submit is allowable. Applicants have also elected the species of T cell stimulation with the understanding that the election, in accordance with 37 C.F.R. §1.142, is for searching purposes only and that upon a finding of allowability of the elected species, the remaining species of T cell inhibition will also be searched.

Accordingly, at the present time, the species election made by Applicants is for search purposes only and Applicants should be permitted to maintain their generic claim while it is established that each species encompassed by the generic claim is allowable

and, thus, that the generic claim is allowable. Applicants should not therefore be required to restrict the claims to the elected species of stimulating T cells, since it has not been established that no generic claims is allowable. Applicants reserve the right to petition the Commissioner to review the requirement under 37 C.F.R. §1.144.

Objection to the Title of the Specification

The Examiner asserts that the title of the present application,"Methods for Modulating T cell Responses by Manipulating a Common Cytokine Receptor Gamma Chain," is not descriptive and "should be restricted to the claimed invention." However, Applicants respectfully traverse this objection since the claimed invention ***is*** drawn to a method of modulating T cell responsiveness, as reflected in the title. As stated in the previous subsection, Applicants should not be required to limit the claims to the elected species (i.e. stimulating a T cell response).

Formal Drawings and Photographs

The Examiner has objected to the drawings and photographs as failing to comply with 37 C.F.R. § 1.84. Applicants will submit formal drawings, including proper photographic figures meeting the requirements set forth in the Notice of Draftperson's Drawing Review, upon payment of the issue fee in the present application as prescribed under 37 C.F.R. §1.84.

Rejection of Claims 98-101, under 35 U.S.C. § 112, First and Second Paragraphs

In paragraphs 6 and 8 of the subject Office Action, the Examiner rejects claims 98-101 under 35 U.S.C. §112 first and second paragraphs. The Examiner asserts that the specification does not contain an adequate written description of "a T cell predetermined to be anergic" as claimed, or define the metes and bounds of this term.

In response, Applicants have amended claim 98 to replace the term "a T-cell predetermined to be anergic" with the term "an anergic T cell." An anergic T cell is an art recognized term which connotes a T cell which, in the absence of a costimulatory signal, has entered a state of unresponsiveness. Evidence of this can be found in numerous publications, such as those submitted herewith as Appendices A and B, where the term "anergy" and "unresponsiveness" are used interchangeably. For example Schwartz et al. (1990) *Science* 24:1349 (previously submitted with Applicants information Disclosure Statement) state that "the T-cell . . . enters an unresponsive state known as clonal anergy" (page 1349). Thus, the authors use the terms "anergy" and "unresponsiveness" interchangeably.

In addition, Applicants' disclosure also makes it clear that the term T cell "anergy" means T cell "unresponsiveness." Specifically, on page 3, lines 1-4, Applicants state that "when stimulated through a T cell receptor (TCR)/CD3 complex without requisite costimulation through the CD28/B7 interaction, T cells enter a state of antigen specific unresponsiveness or anergy." Therefore, the metes and bounds of the term "an anergic T cell" as recited in claims 98-101 would have been clear to one of ordinary skill in the art at the time of the invention based on both Applicants' disclosure and the definition given to this term in the art. Accordingly, requirements of 35 U.S.C. §112, second paragraph, have been met.

Applicants' disclosure also fully enables the subject matter encompassed by claims 98-101. These claims are drawn to a method for modulating responsiveness "in an anergic T cell," comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is modulated. how to make and use an anergic T cell. At page 3 lines 26-29, Applicants teach that "T cells are contacted *in vivo* or *ex vivo* in the presence of an antigen with an agent which inhibits delivery of a signal through the cytokine receptor γ chain resulting in T cell unresponsiveness to the antigen." Applicants also describe several reagents and methods

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which can be used to generate anergic T cells, for example, at page 13, lines 4-38 and page 14 lines 1-16. Applicants also teach how to use anergic T cells as claimed, for example, at page 3 lines 35-37. Moreover, methods for inducing T cell anergy were well known to those of ordinary skill in the art at the time of the invention. Evidence of such can be found, for example, in Johnson et al. (1994) *Life Sciences* 55(23):1767-1780 (submitted herewith as Appendix A), entitled "Minireview: The Role of Anergy in Peripheral T Cell Unresponsiveness" which outlines several art recognized techniques for inducing anergy in *in vitro* systems.

Overall, in view of the teachings provided in Applicants disclosure and the knowledge in the prior art at the time of the invention, one of ordinary skill in the art could have practiced the methods of claims 98-101 without undue experimentation. Accordingly, these claims comply with the requirements of 35 U.S.C. §112, first paragraph, and the Examiner is respectfully requested to withdraw the rejection.

Rejection of Claims 48-61 and 97-101 Under 35 U.S.C. § 112, First Paragraph

Claims 48-61 and 97-101 are rejected under 35 U.S.C. §112, first paragraph, based on the Examiner's assertion that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo."

From the outset, Applicants respectfully submit that the Examiner has changed the grounds for the present rejection from those provided in the previous Office Action for reasons not necessitated by Applicants' amendments. Therefore, Applicants respectfully request that the finality of the present Office Action be withdrawn and that the present Amendment be treated as an Amendment submitted prior to a final Office Action (MPEP 706.07(a)).

In particular, the grounds for rejecting claims 48-61 and 97-101 relied on by the Examiner in the previous Office Action was that "*in vitro* and animal model studies have

not correlated well with *in vivo* clinical trial results in patients and it is not clear that reliance on the *in vitro* experimental conditions accurately reflects the relative efficacy of the claimed therapeutic strategy to stimulate T cells (inhibit unresponsiveness)." The Examiner further stated that "there is no evidence that such an experimental model mimics the clinical situation." Thus, in the previous Office Action, the rejection was based on the Examiner's assertion that Applicants' disclosure fails to enable clinical application of the claimed methods.

However, in the present Office Action, the Examiner no longer relies on an asserted failure by Applicants to enable clinical application of the claimed methods. In fact, the Examiner "agrees" at page 4, lines 6-8, of the Action "that it is unnecessary that appellant must prove the ultimate value in humans of their asserted utility." Rather, the Examiner now states that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo." In particular, the Examiner states that "the issue involved is whether or not the evidence of record, based on in-vitro studies, is generally recognized by those of ordinary skill in the art, as being ***reasonably predictive of success in the practical in-vitro and in-vivo therapeutic methods encompassed by the instant claims***." The Examiner further states that the issue is "whether Applicants specification provides insufficient information or nexus which enables any person skilled in the art to use the full scope of the broadly claimed therapeutic methods of modulating or inhibiting unresponsiveness in T cells."

Applicants essentially have been deprived of an opportunity to respond to the new above-summarized grounds for rejection presented in the present Office Action prior to final. Accordingly, Applicants respectfully submit that the finality of the present Office Action should be withdrawn.

Applicants also respectfully traverse the rejection for at least the following reasons. As asserted in the previous Amendment, the proper standard for judging

enablement of claims involving an asserted therapeutic effect is whether the applicant's disclosure provides sufficient guidance and data which would lead one of ordinary skill in the art to ***reasonably*** believe on face value the asserted utility or effect (*In re Brana* 51 F.3d 1560; 34 U.S.P.Q.2D 1437 (CAFC, decided March 30, 1995). The Court specifically held that if a patent disclosure presents a working description of an invention and data to support its utility which could be reasonably applied to *in vivo* systems, then further evidence should ***not*** be required to satisfy the enablement requirement of section 112, first paragraph, ***unless there is reason to doubt the objective truth*** of the asserted utility. As pointed out in the previous Amendment and further below, Applicants' disclosure fully satisfies this enablement standard.

Moreover, Applicants maintain that the facts and the holding of *In re Brana, supra*. are indeed applicable to the present application. The Examiner states that *In re Brana* can be distinguished from the present case because the facts involved a chemical compounds "which were structurally similar to other compounds known in the art and for which animal models were art recognized to be predictive of therapeutic usefulness." However, Applicants maintain that the Court's holding was intended to apply far beyond the specific chemical compounds claimed in the case.

For example, the CAFC held that the asserted utility for the claimed antitumor compounds, which was credible on its face to one of ordinary skill in the art, was *presumptively* correct and that, "even if the PTO had met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility." In particular, the Court stated that "one who has taught the public to that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans."

As applied to the present application, the enablement standard set forth in *In re Brana* is fully satisfied in that Applicants' disclosure provides more than sufficient guidance on how to make and use the claimed invention and further provides working examples demonstrating the *in vitro* efficacy of the claimed invention which, together, render credible the asserted use of the claimed methods for *ex vivo* or *in vivo* treatment of human disease states.

For example, Applicants provide an *in vitro* working description of the claimed invention using a human T cell model system (*see* e.g., page 21). The data presented therein is more than reasonably indicative of *in vivo* efficacy as asserted and claimed by Applicants. Human T cells and the cell lines described in the disclosure are routinely used to mimic the immune system *in vitro* and are art-accepted models of *in vivo* therapeutic efficacy. recognized techniques.

The Examiner asserts that "scientific reasoning and evidence" has been presented to support the instant rejection that rebuts a reasonable correlation between the *in vitro* data presented by Applicants and *in vivo* efficacy. However, Applicants respectively disagree that the Examiner has provided any evidence at all to support the assertion in the previous Office Action, that *"in vitro and animal model studies have not correlated well with in-vivo clinical trial results in patients."* The Examiner merely made this assertion without any evidence to support it. As confirmed by the Court in *In re Brana*, such ***evidence*** to rebut enablement is required to support a *prima facie* case of lack of enablement. No such evidence has been presented in the present case. Therefore, because Applicants have provided data which more than reasonably supports the asserted *in vitro* and *in vivo* utilities of the claimed invention, the present rejection should be withdrawn.

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Rejection of Claims 48, 56-61 and 98 Under U.S.C. §112 Second Paragraph

Claims 48, 56-61, 98 are rejected under U.S.C. §112 second paragraph as being indefinite and ambiguous in the recitation of the phrases "modulating T cell responsiveness" and "such that the T cell responsiveness is modulated" in the absence of a clear positive or negative effect. In particular, the Examiner states that the term "modulation" is not appropriate because modulation can occur both in positive and negative directions and Applicant elected methods of stimulating T cells.

Applicants respectfully traverse this rejection. The meaning of the term "modulation" is made clear in Applicants' disclosure and is also consistent with the art-recognized definition of this term at the time of the invention. As acknowledged by the Examiner, modulation of a T cell response as claimed by Applicants encompasses both a positive effect (e.g., stimulation) and a negative effect (i.e., unresponsiveness).

Moreover, the fact that Applicants elected a particular species for search purposes only under 37 C.F.R. §1.142 which is encompassed by the term "modulation" is irrelevant to the definiteness of this term. As previously argued, Applicants should not be required to limit the claims to the elected species at this time.

In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

Rejection of claims 48-53, 55-58, 59 60-61, 97-100 Under U.S.C. § 102

Claims 48-53, 55-58, 60-61, 97-100 stand rejected under U.S.C. § 102(e) as being anticipated by Plunkett et al. (U.S. Patent No. 5,382,427). Claims 48-53, 55-61 and 97-100 stand rejected under U.S.C. § 102(b) as being anticipated by Lee et al. (U.S. Patent No. 5,017,691). Claims 48-53, 55-61 and 97-100 stand rejected under U.S.C. § 102(a)(e) as being anticipated by Lynch et al. (U. S. Patent No. 5,229,115). Claims 48-53, 59, 61, 97-100 stand rejected under U.S.C. § 102(e) as being anticipated by Grabstein et al. (U.S. Patent No.5, 474,769). The Examiner asserts that the cytokines and methods of use

taught in each of the aforementioned references meet the limitations of the presently claimed methods, and that the functional limitations recited in the present claims "would be addressed by the inherent properties of the referenced methods."

Applicants respectfully traverse these rejections because none of the aformentioned references teach or suggest the step of detecting a signal via the receptor γ chain as claimed. Moreover, certain references fail to teach or suggest the step of modulating responsiveness in an anergic T cell as claimed (e.g. claims 98-100). Therefore, these references fail to anticipate the methods of the claims 48-53, 55-58, 59 60-61, 97-100 since they do not teach all of the material elements (i.e., steps of the claimed methods) recited in the claims.

Plunkett et al. teach the use of IL-4 to treat solid tumors. Lee et al. teach the use of IL-4 to enhance the natural defense against various infections and malignancies. Lynch teach the use of IL-7 to treat individuals with cancer or viral infections by adoptive therapy. Grabstein et al. teach the use of IL-7 to treat microbial infections in infected mammals.

The Examiner without basis assumes that the result achieved by each of the aformentioned references (e.g. reduction in tumors or inhibition of microbial infections) by administering a cytokine (e.g. IL-4 or IL-7) is indicative of signaling via the receptor γ chain. In other words, the Examiner asserts that the observation of these results is equivalent to or inherently encompasses detecting such signaling as claimed by Applicants. However, Applicants respectfully disagree.

The fact that each reference shows a result achieved by administrating a cytokine is not equal to, or necessarily indicative of, signaling via the cytokine receptor γ chain. Therefore, the teachings of the cited references do not necessarily inherently encompass the step of detecting signaling via the cytokine receptor γ chain One of ordinary skill in the art would appreciate that alternative signaling pathways can be involved in cytokine-mediated tumor reduction and antiviral activity which do not necessarily involve the

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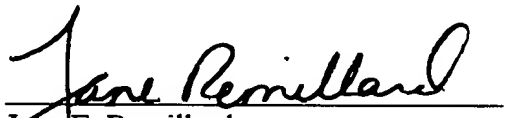
receptor γ chain. Thus, Applicants maintain that not all of the elements of the invention as claimed are taught by the cited prior art references.

Accordingly, Applicants respectfully request the Examiner to withdraw the above-referenced rejections under 35 U.S.C. §102.

Conclusion

In view of the above amendments and remarks, it is believed that the present application is in condition for allowance. If a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call Applicants' attorney at (617) 227-7400 X274.

Respectfully submitted,



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Dated: June 24, 1997